

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 November 2000 (16.11.00)	To: Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No. PCT/US00/04560	Applicant's or agent's file reference MBA1100WO
International filing date (day/month/year) 22 February 2000 (22.02.00)	Priority date (day/month/year) 26 February 1999 (26.02.99)
Applicant SMITH, David, W. et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

23 September 2000 (23.09.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MBA1100WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 04560	International filing date (day/month/year) 22/02/2000	(Earliest) Priority Date (day/month/year) 26/02/1999
Applicant MERCK & CO., INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of Invention is lacking (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-20 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search with respect to Claims 1-20 has been restricted to compounds listed in example 636, i.e. compounds containing the partial structure, 4-C1-C6H4-SO2N(CHMe-R)-Ar, where Ar is 2,5-difluorophenyl, 2,5-dichlorophenyl or 5-chloro-2-hydroxymethylphenyl; and R is any group falling within the definition of G given in Claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/04560

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/21	C07C323/41	C07D211/24	C07D311/20	C07D207/08
C07D277/06	C07D295/12	A61K31/18	A61P25/00	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 03166 A (MONSANTO) 29 January 1998 (1998-01-29) page 3, line 36 -page 4, line 13 ---	1-21, 23, 25, 26
X	WO 98 22104 A (G. PASINETTI, ET AL.) 28 May 1998 (1998-05-28) the whole document ---	1-21, 23, 25, 26
A	US 5 624 937 A (J.K. REEL, ET AL.) 29 April 1997 (1997-04-29) the whole document ---	1, 20, 21, 23, 25, 26
P, X	US 5 981 168 A (P.B. REINER, ET AL.) 9 November 1999 (1999-11-09) the whole document -----	1-21, 23, 25, 26

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 June 2000

Date of mailing of the international search report

06/07/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/04560

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9803166	A 29-01-1998	AU 3890397	A	10-02-1998
		CN 1238688	A	15-12-1999
		CZ 9900168	A	11-08-1999
		EP 0939629	A	08-09-1999
		NO 990247	A	19-03-1999
		PL 331338	A	05-07-1999
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WO 9822104	A 28-05-1998	US 5985930	A	16-11-1999
		AU 5361298	A	10-06-1998
		EP 0956009	A	17-11-1999
		NO 992374	A	21-07-1999
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US 5624937	A 29-04-1997	NONE		-----
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US 5981168	A 09-11-1999	AU 3991999	A	06-12-1999
		WO 9959597	A	25-11-1999
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FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
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CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

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B. FIELDS SEARCHED

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IPC 7 C07C C07D A61K A61P

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X	WO 98 22104 A (G. PASINETTI, ET AL.) 28 May 1998 (1998-05-28) the whole document ---	1-21,23, 25,26
A	US 5 624 937 A (J.K. REEL, ET AL.) 29 April 1997 (1997-04-29) the whole document ---	1,20,21, 23,25,26
P, X	US 5 981 168 A (P.B. REINER, ET AL.) 9 November 1999 (1999-11-09) the whole document -----	1-21,23, 25,26

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 June 2000

Date of mailing of the international search report

06/07/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

English, R

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-20 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search with respect to Claims 1-20 has been restricted to compounds listed in example 636, i.e. compounds containing the partial structure, 4-C1-C6H4-SO2N(CHMe-R)-Ar, where Ar is 2,5-difluorophenyl, 2,5-dichlorophenyl or 5-chloro-2-hydroxymethylphenyl; and R is any group falling within the definition of G given in Claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/04560

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9803166	A	29-01-1998	AU	3890397 A	10-02-1998
			CN	1238688 A	15-12-1999
			CZ	9900168 A	11-08-1999
			EP	0939629 A	08-09-1999
			NO	990247 A	19-03-1999
			PL	331338 A	05-07-1999
WO 9822104	A	28-05-1998	US	5985930 A	16-11-1999
			AU	5361298 A	10-06-1998
			EP	0956009 A	17-11-1999
			NO	992374 A	21-07-1999
US 5624937	A	29-04-1997	NONE		
US 5981168	A	09-11-1999	AU	3991999 A	06-12-1999
			WO	9959597 A	25-11-1999

PATENT COOPERATION TREATY

14

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REC'D 11 APR 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MBA1100WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/04560	International filing date (day/month/year) 22/02/2000	Priority date (day/month/year) 26/02/1999
International Patent Classification (IPC) or national classification and IPC C07C311/21		
Applicant MERCK & CO., INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 23/09/2000	Date of completion of this report 09.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herzog, A Telephone No. +49 89 2399 8033



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/04560

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-367 as originally filed

Claims, No.:

1-26 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/04560

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- the entire international application.
- claims Nos. .

because:

- the said international application, or the said claims Nos. 21-26 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-20 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 1-20.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/04560

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/04560

R Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 21-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 21-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. Claims 1-20 were found unsearchable. The claims are so broad that a very large number of documents relevant to the issue of novelty was found. The search therefore had to be restricted to compounds listed in example 636, i.e. to compounds containing the partial structure 4-Cl-C₆H₄-SO₂N(CHMeR)Ar, wherein Ar is 2,5-difluorophenyl, 2,5-dichlorophenyl or 5-chloro-2-hydroxymethylphenyl; and R is any group falling within the definition of G given in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

3. Moreover, the present claims 1-20 do not meet the requirements of Article 6 PCT in the following respects:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/04560

3.1 Expressions such as "ester", "carboxylate", "amide", "amine", "ether", "sulfonyl", "sulfonamide" and "sulfonamidyl" used in claims 1, 5 and 17 are vague and indefinite since they only define a part of the residue, while the residue connected to such a functional group remains undefined. The expressions therefore render the scope of the claims unclear.

Some of the expressions are defined in the specification. However, the claims have to be clear from the wording of the claims alone.

3.2 The expression "substituted" used in claims 1-19 without a further definition of possible substituents is vague and indefinite and therefore renders the scope of the claims unclear. Moreover, it is clear to the person skilled in the art that not any substituent could be present in compound used in pharmaceutical compositions and thus solve the problem posed (Article 33(3) PCT).

3.3 The expression "lower alkyl" used in claims 2 and 7-19 is vague and indefinite and renders the scope of said claims unclear.

3.4 In the general formula in claim 1, the meaning of C is not clear. In the case that C is a variable, the definition of the variable is missing. In the case that C represents a carbon atom, the carbon atom is connected to 3 atoms only; one substituent is missing.

4. The present general formula in claim 1 consists of a sulfonamide group, a substituted carbon atom which is connected to the nitrogen atom of said sulfonamide group, and 4 further variables. This general formula encompasses a multitude of theoretically possible compounds generated by the mutation of the 4 variables.

No characterizing pharmacophore is thus defined nor can it be found in such a general formula.

It is a well-known and recognized principle in the field of pharmacology, especially in enzyme pharmacology, that a compound must have a very characteristic and specific structure to be active as an inhibitor or agonist. Already small changes in the structure of a compound can lead to fundamental changes in activity.

It is thus clear for the skilled person that in the absence of any characterizing pharmacophore, not all of the compounds according to the general formula in

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/04560

claim 1 act as inhibitors and represent a solution to the underlying problem (Article 33(3) PCT).

The scope of the present claims is thus far too broad in scope and has to be restricted accordingly.

5. As already explained above, the search had to be restricted to compounds listed in example 636 with the structure 4-Cl-C₆H₄-SO₂N(CHMeR)Ar, wherein Ar is 2,5-difluorophenyl, 2,5-dichlorophenyl or 5-chloro-2-hydroxymethylphenyl; and R is any group falling within the definition of G given in claim 1.

The examination therefore has been carried out for said compounds only.

D1: WO 98 03166 A

D2: WO 98 22104 A

D3: US-A-5 624 937

- 5.1 None of the documents D1-D3 discloses compounds identical or similar to the compounds of the invention with the structure 4-Cl-C₆H₄-SO₂N(CHMeR)Ar wherein Ar is 2,5-difluorophenyl, 2,5-dichlorophenyl or 5-chloro-2-hydroxymethylphenyl; and R is any group falling within the definition of G given in claim 1.
- 5.2 In the in vitro cell-based assay of inhibitors of Amyloid β production (Example 636 on pages 311 ff.), compounds which fall within the searched formula 4-Cl-C₆H₄-SO₂N(CHMeR)Ar are listed in the table which do not display measurable activity (cf. page 350, compound nr. 1098 and page 359, compounds nr. 1292, 1293 and 1296) and therefore do not solve the problem posed, contrary to the requirements of Article 33(3) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/04560

Re Item VI

Certain documents cited

D1: US-A-5 981 168 (P.B. Reiner et al.) 9 November 1999

Re Item VIII

Certain observations on the international application

The vague and imprecise statement in the description on page 367, lines 5-7 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).